Peer Review
Experimental Toxicology Division
N H E E R L

MODELING

Dosimetry Modeling as an Integrated Component of Exposure-dose-response Modeling for Volatile Organic Hazardous Air Pollutants

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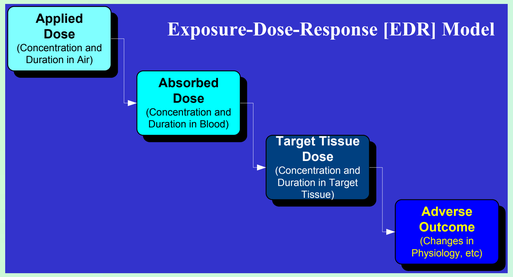
ENVIRONMENTAL ISSUE

- EPA must often assess the health risk of exposure conditions for which animal or human data are not available. In these situations, adjustments (i.e. extrapolations) are made from situations where data exists to the situations of interest to the Agency.
- The standard method for exposure-duration adjustment for acute inhalation exposure is based on Haber's Rule:
  C (Concentration) x t (exposure duration) = K (a constant toxic effect).
- Physiologically-based pharmacokinetic (PBPK) modeling is a promising alternative method for dose-duration adjustment

OBJECTIVE

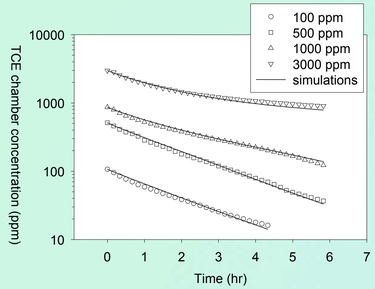
- The overall purpose of this project is exploration of the relationship between external exposure concentration, internal dosimetry and neurological effect for those volatile organic chemicals (VOCs) included in the Clean Air Act Amendments list of 188 hazardous air pollutants that are subject to residual risk determinations, or are of concern for indoor air or mobile sources..



Within an EDR model, PBPK modeling is used to move from applied dose to absorbed dose and from absorbed dose to target tissue dose.

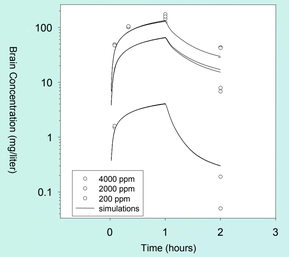
We have developed a PBPK model with specificity for the Long-Evans rat as it is the rodent stock being used for neurological assessment of VOCs at NHEERL.

Experiment to Determine Metabolic Rate Constants for TCE in male Long Evans rats.

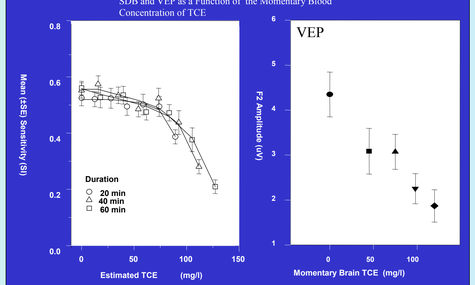


Closed chamber experiments were conducted in ETD's single-animal gas uptake system. With Km held constant at 0.25 mg/L, optimization for VmaxC resulted in a value of 8.68. mg/hr/kg.

Comparison of Brain TCE Concentrations Measured in Long Evans Rats and Predicted with our PBPK Model

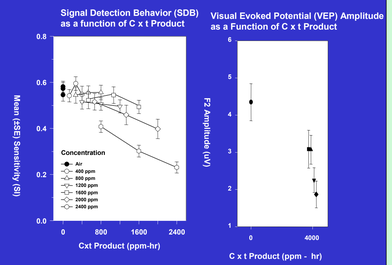


Does internal dosimetry predict the acute neurotoxic effects of TCE?

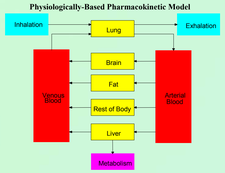


In contrast to Haber's Rule which did not predict the acute neurotoxic effects of TCE, the blood concentration of TCE at the time of neurotoxicity testing (momentary TCE concentration) was predictive. As expected, given the close correlation between blood and brain TCE concentration, the momentary brain concentration of TCE (not shown) predicted neurotoxic outcome. However, other measures of internal dose, such as blood AUC were not predictive.

Does Haber's Rule Predict the Acute Neurotoxicity of VOC's?



In the male Long-Evans rat, a linear form of Haber's Rule did not predict the acute effects of inhaled trichloroethylene (TCE) on either signal detection behavior (a behavioral assessment of sustained attention) or the rat visual system (visual evoked potentials). If Haber's rule were to hold, the effects at each C x t product should be equivalent and they are not. Similar results have been seen with toluene and perchloroethylene.



TCE PBPK Model Input Parameters.

Parameters	Model Input
Long Evans Rat Specific	
Body weight (BW)	350.0 to 461.4 gm
Fat volume (VFC)	$y=-3.9889x10^{-6}(BW)^3 + 0.0062(BW)^2 - 2.7643(BW) + 407.61$
Liver volume (VLC)	y = 0.0286(BW) + 4.0216
Brain volume (VBC)	y = -0.00083(BW) + 0.8257
Partition coefficients	
blood/air	20.69
brain/air	14.58
liver/air	21.34
fat/air	470.00
rapidly/air	21.34
slowly/air	12.36
VmaxC (mg/hr/kg)	8.68
Km (mg/L)	0.25
Input Parameters Without Specificity to the Long Evans Rat	
Slowly perfused volume fraction (VSP)	70%
Rapidly perfused volume fraction (VRP)	91% -VFC -VLC - VBC - VSP
Input Parameters with Specificity for the F-344 Rat	
Ventilation Rate (QPC)	10.5
Cardiac Output (QCC)	11.2
Fat Blood Flow Percentage (QFC)	8.2%
Liver Blood Flow Percentage (QLC)	24.2%
Brain Blood Flow Percentage (QBC)	2.7%
Slowly Perfused Blood Flow Percentage (QSC)	25.7%
Rapidly Perfused Blood Flow Percentage(QRC)	100 -QFC - QLC - QBC – QSC

The Long Evans specific parameters were measured as part of this project. Long-Evans blood flows are currently being measured for this project in the laboratory of Dr. Michael Delp.

In the absence of Long Evans specific blood flows, blood flow values from F-344 rats were used as they were found to provide better fits to both the Long-Evans gas uptake and tissue concentration data than flows from SD rats.

The Long Evans rat PBPK model for TCE provided better fits to both vapor uptake data and tissue concentration data than did a previous PBPK model for TCE

Index of the Discrepancy Between Model Simulations and Experimental Data.

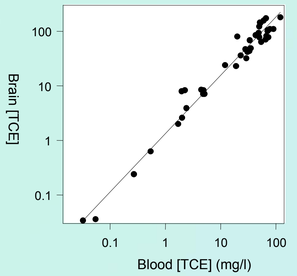
Parameter	Present Model	Andersen et al. (1987)
Vapor Update Data	0.05	0.14
Blood Data	1.16	1.60
Fat Data	0.98	2.81
Liver Data	0.20	0.68
Brain Data	0.26	0.72[d]
Cannulated Blood Data	1.02	1.39
Combined Index	0.48	0.88

The indices were calculated by the methods described by Krishnan et al. (1995).

The Andersen et al. (1987) model did not include a separate compartment for the brain. A brain compartment was added to the Andersen et al. model by using the liver PC from the Andersen model for the brain PC. Brain volume and blood flow were from the present model.

The combined index is the weighted average of the indices derived from the 6 individual data sets (vapor uptake, blood, fat, liver, brain, cannulated blood)

Blood vs Brain [TCE]



There is a close linear relationship between the concentration of TCE in blood and the concentration of TCE in brain, $r^2 = 0.974$

IMPACT

- We have provided information on duration adjustments to the Office of Air Quality Planning and Standards, the Office of Transportation and Air Quality, the National Center for Environmental Assessment and EPA regional risk assessors.
- We have developed, proposed and implemented an alternative approach for exposure-duration adjustment, with PBPK modeling used to estimate relevant internal dose.
- Dose-based duration adjustments represent an improvement in assessment of health risk that can be applied in a number of situations.
- We used this approach to assist the National Advisory Committee to the National Research Council that is developing Acute Exposure Guideline Levels (AEGLs) for TCE.

FUTURE DIRECTIONS

- Mechanistic evaluation of momentary blood/brain concentration of the parent chemical as an appropriate dose metric for the acute effects of VOCs.
- Animal-to-human extrapolation based on internal dose, with an emphasis on toluene, one of the few VOCS to which human volunteers can be exposed (in collaboration with HSD).
- Evaluation of mixtures of VOCs by a relative-potency-factor approach with dose being blood or brain concentration estimated by appropriately parameterized PBPK models.
- Implementation of multi-route PBPK models to estimate the contribution of additional routes of exposure (oral, dermal) on target tissue dose.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SOLVING AGENCY PROBLEMS